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T he endocrine system works in conjunction with the nervous system to regulate, and coordinate the activities of, the body's tissues and organs. It consists of a collection of glands located in different parts of the body – the main ones being the pituitary, pineal, thyroid, parathyroids, adrenals, pancreas, ovaries and testes. These glands produce a variety of blood-borne chemical signals called hormones, which play an essential role in maintaining balance (homeostasis) in the body, helping to ensure that variables such as blood glucose and electrolytes are kept within normal ranges.

Pituitary gland and somatopause

The pituitary gland, often referred to as the master gland, produces several major hormones and regulates the activity of many other endocrine glands. It is split into a posterior portion, which is formed from neural tissue extending from the hypothalamus, and an anterior portion, which is formed from epithelial cells derived from the roof of the oral cavity.

The anterior pituitary secretes growth hormone (somatotropin), which promotes the growth of bone, muscle and most of the major internal organs. In early childhood, somatotropin is secreted in relatively small amounts, but during the teenage years there is a marked increase in serum somatotropin levels corresponding to the growth spurts of puberty. Around the age of 25-30, somatotropin secretion begins to decline in both men and women. In men it is estimated to halve every seven years – although there appears to be much variation between individuals (Gentili, 2015).

The decline in somatotropin secretion in later years is often referred to as the somatopause and is associated with a variety of physiological changes (Jonas et al, 2015; Veldhuis et al, 2005), including:

- A general reduction in protein synthesis;
- An increase in fat mass from the accumulation of adipose tissue;
- A reduction in muscle mass; and
- Sleep disturbances.

These changes can lead to the build-up of body fat, lower bone density, impaired blood glucose control and sleep disturbances.

Age-related changes to the endocrine system increase the risk of insomnia, fractures, type 2 diabetes and cognitive decline. This seventh article in our series about the effects of age on the body describes what happens, with advancing age, to endocrine glands and hormone production.
Pineal gland and sleep disturbances

The pineal gland is slightly smaller than a pea and resembles a small pine cone—hence its name. Found in the diencephalon, towards the centre of the brain, it synthesises the hormone melatonin from the neurotransmitter serotonin. The pineal gland functions like an internal body clock: during the day, when there is a lot of light, melatonin secretion is inhibited, but as the day draws to a close and light diminishes, melatonin secretion increases, preparing the body for sleep.

As we age, the pineal gland undergoes a process of calcification, detectable even in young children. Melatonin levels progressively decrease: 60-year-olds have 80% less melatonin in their blood than teenagers. Some drugs commonly prescribed to older people, such as beta blockers and non-steroidal anti-inflammatory drugs, can reduce melatonin levels even further.

Decreased melatonin levels are linked to an increased prevalence of sleep disturbances and, in some people, may ultimately lead to geriatric insomnia (Rubenik and Konturek, 2011). Since sleep is essential for cognitive function, sleep disturbances can exacerbate age-related changes in the brain.

There is some evidence that exposure to bright light—either sunlight or artificial light—in the morning increases the speed of sleep onset by triggering an earlier release of melatonin in the evening. Similarly, the therapeutic use of prolonged-release melatonin has been shown to improve sleep onset time, sleep quality, morning alertness and quality of life in people aged 55 and over who have insomnia (Wade et al, 2007).

The thyroid gland and metabolism

The thyroid gland plays a major role in controlling metabolism and adjusting blood calcium levels. The hormones it secretes regulate a number of physiological processes, including:
- The metabolism of carbohydrates, fats and proteins;
- Thermoregulation;
- Digestion;
- Muscle and nerve activity;
- Maintaining skin thickness and integrity;
- Maintaining normal bone density.

Changes to metabolic rate

The thyroid secretes the iodine-containing hormones T4 (tetraiodothyronine, which is also known as thyroxine) and T3 (triiodothyronine), which largely control cellular metabolism. T4 is released in greater quantities than T3, the typical ratio being 15:1. T4 is then rapidly converted into the more biologically active T3, which is around three times more potent in terms of increasing the metabolic rate.

The clearance of T4 by the liver decreases with age, but this is offset by a gradual decline in T4 secretion, so T4 serum levels tend to remain constant. However, there is a clear age-related decrease in the levels of serum T3, as well as of thyroid-stimulating hormone (TSH) produced by the pituitary gland (Peeters, 2008; Chahal and Drake, 2007). This may contribute to the gradual reduction in basal metabolism that is apparent in many people in middle and old age (in which the decline in lean muscle mass described above also plays a role).

With advancing age, autoimmune reactions against one’s own thyroid gland are commonly seen. Indeed, the presence, in older people, of antibodies specific to thyroid tissue is so common that it is often considered a normal age-related change. A high concentration of such antibodies may herald the onset of autoimmune hypothyroidism, a disease affecting up to 5% of the population.

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Systems of life

- A progressive reduction in lean body mass (muscle) contributing to a decline in metabolic rate;
- An increased deposition of adipose tissue, particularly abdominal fat (‘middle-age spread’);
- A reduction in bone mass and density leading to an increased risk of osteoporosis and fractures;
- A general decrease in immune function and higher susceptibility to infection.

The somatopause can be hastened in people who lead a sedentary lifestyle and in those who already carry a high percentage of body fat. Conversely, in premenopausal women, oestrogen appears to slow its onset and progression (Gentili, 2015).

The exact causes of somatopause are yet to be fully established, however, the age-related decrease in somatotropin secretion mirrors the decrease of growth-hormone releasing hormone (GHRH) secretion by the hypothalamus. Recent research indicates that some of the negative physiological changes that come with declining levels of somatotropin can be reversed by growth hormone replacement therapy. In clinical trials, recombinant human growth hormone has been shown to improve lean muscle mass retention and quality of life scores in older people (Jonas et al, 2015).
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Systems of life

over-60s and associated with low metabolic rates, a tendency to put on weight and low core temperature. Since this condition is autoimmune in nature, women are at greater risk of developing it (this is true for most autoimmune diseases); up to eight times more women than men experience autoimmune hypothyroidism.

The results of thyroid function tests should be assessed carefully in older people, as common long-term conditions (such as chronic obstructive pulmonary disease, hypertension, diabetes and arthritis) and dieting can lead to reductions in circulating thyroid hormones, particularly the more active T3. This phenomenon of reduced thyroid function in the absence of thyroid disease is referred to as non-thyroidal illness. Similarly, many drugs used to treat long-term conditions in older people (for example, lithium and glucocorticoids) can suppress thyroid function or reduce the activity of circulating thyroid hormones, leading to a reduction in metabolic rate (Peeters, 2008).

Changes to calcitonin secretion

The thyroid gland also plays a role in calcium homoeostasis. When we consume foods rich in calcium, it releases calcitonin, which inhibits the activity of osteoclasts – bone cells that break down bone tissue (bone is a dynamic tissue continually being built and broken down). By inhibiting osteoclast activity, calcitonin indirectly increases bone density.

Few studies have examined the effects of ageing on calcitonin production in humans. The most comprehensive study, dating back to 1980, demonstrated an age-related decline in calcitonin production in 50 healthy women aged between 20 and 69 years (Shamoni et al, 1980). This decline may partially explain the reduction in bone mass seen in most women as they grow older. However, a later study has contradicted these findings, showing that although women appear to have lower levels of calcitonin secretion than men, there is no clear age-related decrease in serum calcitonin concentration (Tiegs et al, 1986).

Parathyroid glands and hyperparathyroidism

The posterior portion of the thyroid is the location of four tiny parathyroid glands, which secrete parathyroid hormone (PTH) whenever blood calcium levels fall. Since a normal concentration of calcium is essential to many physiological processes (including muscle contraction, nerve conduction and blood clotting), the reserves of calcium stored in the skeleton need to be mobilised. PTH triggers the release of calcium from the bones into the blood by indirectly stimulating osteoclasts.

Several studies have shown that most people, as they grow older, have significantly increased levels of circulating PTH (Portale et al, 1997). This hyperparathyroidism may well be one of the main causes of the reduction in bone density commonly seen in middle and old age. Recent studies have also shown a potential link with other pathologies, particularly age-related cognitive decline and dementia (Braverman et al, 2009).

The pancreas and diabetes risk

The endocrine regions of the pancreas (islets of Langerhans) regulate blood glucose levels. Beta cells in the islets secrete insulin in response to increased blood glucose – for example, after a carbohydrate-rich meal. Insulin binds to receptors present on most cells, triggering the uptake of glucose from the blood. Once inside the cells, glucose is either metabolised immediately to release energy, or stored and converted into glycogen.

Alongside race, genetic predisposition and a high body mass index, ageing is one of the many risk factors linked to the development of type 2 diabetes (Knight and Nigam, 2017). Ageing human cells become less sensitive to the effects of insulin. The most likely cause appears to be a reduction in the number of insulin receptors at the surface of cells. This gradual insulin resistance goes hand in hand with an increase in blood glucose concentrations.

As shown in a study of 6,901 non-diabetic people (Ko et al, 2006), fasting blood glucose levels rise by around 0.15mmol/l for each decade of life after the age of 20. Whether this rise is a normal age-related change or a sign of diabetes in its early stages is not always clear, but it is certainly seen in many older people with no other symptoms of diabetes.

With advancing age, the insulin-producing beta cells become less sensitive to the level of glucose in the blood, so higher blood glucose levels are needed to trigger insulin release. Since older people’s cells are less receptive to insulin, the pancreas often responds by producing more, leading to increased insulin levels in the blood (hyperinsulinaemia). This can put excessive stress on the beta cells, leading to their exhaustion.

Age-related depletion of the beta cell population in the pancreas also occurs as a result of increased programmed cell death (apoptosis) and a diminished ability of the pancreas to produce new cells. Beta cell exhaustion and depletion result in a drop of insulin secretion of up to 0.5% per year of life. Additionally, the clearance of insulin by the liver increases with age, so there is less insulin available to interact with cells and promote glucose uptake.

These age-related changes to insulin production, clearance and response contribute to the creation of a diabetogenic environment. This may partially explain why the risk of developing type 2 diabetes increases with age (Brown, 2012).

Abdominal fat

The accumulation of abdominal fat is a common feature of ageing, particularly in people who have a poor diet and/or a sedentary lifestyle. Many age-related changes to the endocrine system contribute to this accumulation of adipose tissue, including the somatopause, autoimmune hypothyroidism, insulin resistance, and reduced circulating sex hormones.

This abdominal fat accumulation is linked to heart disease, high blood pressure and type 2 diabetes. These conditions may occur in isolation or together in the form of metabolic syndrome (Gong and Muzumdar, 2012).

The adrenal glands

The two adrenal glands are located above the kidneys and each consists of two main regions: the adrenal medulla (inner region) and the adrenal cortex (outermost layer).

Adrenal medulla and adrenaline

The adrenal medulla is the location of chromaffin cells, which secrete the catecholamines adrenaline (epinephrine) and noradrenaline (norepinephrine). These are the ‘fight or flight’ hormones that prepare the body for activity when it is threatened or in a state of excitement. The effects of adrenaline and nor-adrenaline include:

- Increased heart rate;
- Increased vasoconstriction in the skin and gut;
- Increased blood pressure;
- Increased blood flow to the major skeletal muscle groups;
- Increased blood flow to the brain;

80% Reduction in melatonin levels in 60-year-olds compared with teenagers
Dilatation of pupils;
• Increased breathing rate and airway dilatation;
• Increased breakdown of liver glycogen resulting in increased blood glucose.

Ageing is associated with a decline in the secretion of adrenaline, but adrenaline plasma levels remain relatively constant as clearance by the kidneys is usually reduced. There is some evidence that older men secrete less adrenaline in response to acute stress than younger men (Seals and Esler, 2000).

Adrenal cortex, aldosterone and cortisol

The adrenal cortex synthesises a variety of steroidal hormones from cholesterol, mainly aldosterone and cortisol.

Aldosterone

Aldosterone is a mineralocorticoid that regulates plasma levels of sodium and potassium, and plays an important role in water balance and blood pressure control. Research has revealed an age-related decrease in serum aldosterone levels, effectively reducing the body’s ability to retain sodium.

Decreased aldosterone secretion may contribute to postural hypotension and the light-headedness that is often experienced by older people when they stand up. This is supported by research demonstrating significant reductions in serum aldosterone levels in older people when they are upright, as opposed to recumbent (Hegstad et al, 1983).

Since sodium attracts water into the cardiovascular system via osmosis, lower plasma sodium levels (hyponatraemia) can lead to reduced blood volume and blood pressure. Several medications commonly prescribed to older people – such as opiates, non-steroidal anti-inflammatory drugs, diuretics and antidepressants – can exacerbate hyponatraemia (Liamis et al, 2008). Blood volume and blood pressure may be further reduced by age-related increases in the secretion of atrial natriuretic hormone (ANH), a powerful diuretic produced by the heart (Miller, 2009).

Cortisol

Cortisol is a glucocorticoid and its release is triggered by biological stressors such as physical injury or starvation. It is a natural anti-inflammatory and plays an important role in the breakdown of protein and fat.

Research into how cortisol levels change with ageing is often contradictory. Initial studies suggested that there could be a 20-50% increase in the mean levels of cortisol secretion between the ages of 20 and 80 (Chahal and Drake, 2007). More recently, however, it has been shown that this is not necessarily true: in some people, cortisol secretion diminishes with age, in others levels remain relatively stable throughout life (Wolf, 2015).

There appears to be a link between increased cortisol levels, reduced bone density and increased risk of bone fracture. There is also growing evidence that a higher cortisol concentration can contribute to the loss of cells from the hippocampus, resulting in hippocampal atrophy. This is often associated with a reduction in cognitive function in older people (Chahal and Drake, 2007). Other studies have shown that age-related increases in cortisol may also be linked to memory loss and sleep disorders (Chahal and Drake, 2007; Wolf et al, 2005).

Ageing of the endocrine system

There is some evidence that exercising regularly and maintaining a low percentage of body fat may slow the onset of the somatopause, help maintain bone density and improve the control of blood glucose. Supplementation with synthetic growth hormone has recently been shown to increase lean muscle mass in older people. However, this kind of therapy is associated with many side-effects such as joint pain, oedema and impaired glucose tolerance (Jonas et al, 2015).

The most famous and most thoroughly researched hormone replacement therapies are those that are used to treat the complications of the menopause. These therapies will be explored in the next article in this series.

References

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